UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,843	03/08/2007	**Alan Olstein**	21001.002PCT	7439

25005 7590 02/27/2008

Intellectual Property Dept.
Dewitt Ross & Stevens SC
2 East Mifflin Street
Suite 600
Madison, WI 53703-2865

EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	**PAPER NUMBER**
1641	

MAIL DATE	DELIVERY MODE
02/27/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,843	OLSTEIN, ALAN	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/6/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/20/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

1. Claim 1-29 are pending and are examined on merits.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 13 recites the phrase “aging the substrate at room temperature in the presence of proteins". It is not clear what “proteins” are encompassed by the term "proteins" in this phrase. The term "proteins" has not been defined in the specification. Specification discloses protein A containing particle (page 8, lines 18-19) and describes the following in page 12: “chemiluminescent substrate described herein exhibit greater sensitivity if the substrate is “aged” in the presence of proteins (generally) and in the presence of heat-denatured proteins (specifically)”. The nature and structure of the “proteins” is not clear from this disclosure. The term “protein” includes antibody, avidin and other specific binding proteins as well. Are they included in the definition of “proteins”?

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-2, 7-8, 10-12, 17-19, 24-25, 27-28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1).

Basbøll *et al* in a method of detecting microorganism in a sample disclose capturing the microorganisms in the sample with an antibody which is bound to a solid phase and detecting the microorganism using any method per se, including detection directly on the solid phase (column 3, lines 49-55). Basbøll *et al* disclose that the antibody coated solid surface may be microparticles, microwell, a test tube, a dipstick, foams, meshes, membranes or other materials commonly used in diagnostic procedures (i.e. antibody adhered to a surface) (column 2, lines 63-67

and column 3, lines 63-67). Basbøll *et al* disclose *Listeria monocytogenes* (i.e. a *Listeria spp.*) (see claim 6) as a specific microorganism to be detected using an anibody specific to *Listeria* cells (i.e. capable of capturing *Listeria spp.* cells; see claim 8).

Basbøll *et al* disclose that the captured microorganism (e.g. *Listeria spp.*) on the solid phase (column 3, lines 54-55) may be detected by using a second antibody labeled with horseradish peroxidase (e.g. ELISA method) (column 5, lines 35-39; column 7, lines 52-65 and column 10, lines 41-64) but, however, fail to disclose detection of the immobilized Listeria spp. cells directly using a substrate for beta-glucosidase and an enhancer molecule.

Bronstein *et al* disclose detection of cells by directly detecting an endogenous enzyme produced by the cells using a substrate for the enzyme (column 1, lines 10-16) wherein the detection involves incubation of the cells producing an enzyme with the enzyme substrate and an enhancer and detection of the chemiluminescent produced by degradation of the substrate by the endogenous enzyme (Column 3, line 60 to column 4, line 5 and column 11, lines 59-67). Bronstein *et al* disclose the endogenous enzyme useful in the invention comprise proteins having enzymatic activity that degrades a substrate to produce a light signal (column 6, lines 1-4). Several enzymes including beat-glucosidase and corresponding substrates are disclosed (column 6, lines 19-64). Brostein *et al* also disclose beta-glucosidase and specific substrate for the enzyme which comprises dioxetane (column 6, lines 56-61). Bronstein *et al* further disclose that the chemiluminescent 1,2 dioxetane

substrate provides high sensitivity in chemiluminescent detection (column 1, lines 50-53) and the chemiluminescent assay provides superior alternative to traditional calorimetric, fluorescent and radioisotopic detention methods (column 1, lines 53-56). Bronstein *et al* also disclose that the use of 1,2 dioxetane substrates provides sensitive, versatile and facile chemiluminescent assay systems for quantification of endogenous cellular enzymes (column 4, lines 1-5).

Chen *et al* disclose that Listeria spp. (e.g. Listeria monocytogenes) possess β-glucosidase activity (column 11, lines 17-18) that can be detected using a β-glucosidase substrates (column 3, lines 50-52).

Therefore, given the above facts that cells possessing an enzymatic activity can be detected directly using a substrate for the enzyme (Bronstein *et al*), which requires less reaction steps than conventional ELISA methods (i.e. ELISA requires additional labeling with second labeled antibody) and *Listeria spp.* possesses a β-glucosidase activity (Chen *et al*) that can be detected with a sensitive 1,2 dioxetane substrate and an enhancer (Bronstein *et al*), one of ordinary skill in the art at the time the invention was made, would have been motivated to detect the immobilized *Listeria spp.* of Basbøll *et al* directly on the solid surface using the β-glucosidase substrate and the enhancer as taught by Bronstein *et al*, with the expectation of detection of the immobilized *Listeria* microorganism quickly (i.e. with less steps) with high sensitivity, with a reasonable expectation of success. In addition the motivation to combine the references also comes from the disclosure that the solid phase bound *Listeria spp*. may be detected by any method, including detection directly on

the solid phase (Basbøll *et al*; column 3, lines 49-55) and from the disclosure that microorganisms possessing enzymatic activity can be detected directly using a highly sensitive 1,2 dioxetane substrates and an enhancer (Bronstein *et al*). In addition, one of ordinary skill in the art at the time of the invention would have a reasonable expectation of success in detecting the immobilized *Listeria monocytogenes* cells of Basbøll *et al* with the 1, 2 dioxetane substrate of Bronstein *et al*, because *Listeria monocytogenes* cells posses a β-glucosidase activity (Chen *et al*) and Bronstein *et al* disclose specific substrates for β-glucosidase enzyme which is highly sensitive (column 6, lines 56-61).

With regard to dependent claim 2, Basbøll *et al* disclose solid phase materials comprising microparticles (column 2, line 65 and claim 14).

With regard to claim 7, Basbøll *et al* disclose using antibody specific for a *Listeria* species (see claim 6).

Regarding claim 8, Bronstein *et al* disclose beta-glucosidase and a substrate for the enzyme comprising 1,2-dioxetane (column 6, lines 56-60).

Regarding claims 10-12, Bronstein *et al* disclose several enhancer molecules (column11, line 59 to column 14, line 60) which reads on the enhancer molecules of claims 10-12 {As for example, compare formula (II) and (III) of Bronstein with the enhancer of Formula I and formula II of instant claim 12}

As for claim 17, Basbøll *et al* disclose washing step to remove non-specifically bound material after incubation of the antibody coated solid phase with the sample comprising microorganism (column 3, line 65 to column 4, line 1), which reads on

step of separating the surface from the sample after step (b) and prior to step (c) of claim 17.

As for kit claims 18-19, 25 and 27-29, Bronstein et al disclose a kit comprising solid surface bound to microorganism specific antibody for the detection (column 5, lines 10-15). However, the packaging of components in kit form is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

8. Claims 5 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) as described above and further in view of Prober *et al* (US 2005/0019842 A1).

See above teaching of Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) for chemiluminescent detection of microorganisim (e.g. *listeria spp.*) using antibody bound to a solid phase and wherein the solid phase may be a microparticles (Basbøll *et al;* column 2, line 65 and claim 14).

Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) differ from the instant application in failing to disclose that the particle is dextran coated particle.

Prober *et al* disclose microparticles-bound capture probes (e.g. antibody bound microparticle) to capture and separate desired analytes (e.g. microorganism) in a sample for detection and analysis (see Fig. 1 and paragraph [0153]). Prober *et al* also disclose that coating the surface of the microparticle with a thin film of hydrophilic polymer such as dextran (paragraph 0230]) resist non-specific binding (paragraph [0230]).

Therefore, given the above fact that microparticles coated with dextran helps to resist non-specific binding (Prober et al), it would have been obvious to one of ordinary skill in the art at the time the invention was made to coat the microparticle of Basbøll *et al* with dextran, with the expectation of reducing non-specific binding of the microparticle, with a reasonable expectation of success.

9. Claims 3-6 and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) as described above and further in view of Giaever (US 3,970,518) and Gruttner *et al* (J. Magnetism and Magnetic Materials 2001).

See above teaching of Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) for chemiluminescent detection of microorganisim (e.g. *listeria spp.*) using antibody bound to a solid phase and wherein the solid phase may be a microparticles (Basbøll *et al;* column 2, line 65 and claim 14).

Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) differ from the instant application in failing to disclose

that the particle is magnetic particle or particles coated with silica, dextran or silica-dextran.

Giaever discloses magnetic particle coated with antibody for separation and detection of bacterial and other cells (see abstract and column 1, lines 5-10). Giaever discloses that magnetic particle is very useful because antibody layer provides a large and widely-distributed surface area for capture of bacterial and other cells (see abstract) and the captured cells from a mixed population can be readily concentrated/separated by applying magnetic field (column 2, lines 30-34 and claim 1).

Gruttner *et al* disclose magnetic particles with improved properties useful for applications in diagnostics, moeculear biology and biomedicine (see abstract). Gutter *et al* disclose that Magnetic particle coated with silica are very efficient to adsorb biomolecules (e.g. proteins, DNA etc.) on their surface (page 1, third paragraph of right column). Gruttner *et al* disclose that magnetic particle coated with silica drastically increases coating ability of a protein (page 5, lines 1-3 of left column). Gruttner et al disclose magnetic nanoparticle with a silicon fortified dextran matrix (i.e. silican and dextran coated particle) with increased protein binding ability (page 5, paragraph 4). Gruttner *et al* also disclose that the silica-fortified magnetic nanoparticles have improved mechanical properties for analytical applications of the magnetic tarticles with a high diffusion speed when compared to non-modified dextran nanoparticles (see paragraph 4).

Therefore, given the above fact that magnetic particle carrying specific recognition molecules are very useful for quick separation of captured cells from a mixed cell population (Giaever), it would have been obvious to one of ordinary skill in the art at the time the invention was made, to substitute the microparticle of Basbøll *et al* with equivalent magnetic particles of Giaver *et al* for quick separation Listeria cells from other cells in the sample using magnetic field for subsequent detection and analysis, with a reasonable expectation of success. Since, silica coated and silica-dextran coated magnetic particles are disclosed to have high binding ability for proteins (e.g. antibody) that have improved mechanical and analytical properties (Gruttner *et al*), it would also be obvious to one of ordinary skill in the art at the time of the invention, to try other known equivalent magnetic particles such as the silica and silica-dextran coated particles of Grutnner for obtaining a magnetic particle suitable for binding of *Listeria* antibody that provides optimal separation and detection of *Listeria* cells.

10. Claims 9 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) as described above and further in view of Giri *et al* (US 6,767,716 B2).

See above teaching of Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) for chemiluminescent detection of microorganisim (e.g. *listeria spp*.) using antibody bound to a solid phase and wherein the solid phase may be a microparticles (Basbøll *et al;* column 2, line 65 and

claim 14). Basbøll *et al* in view of Bronstein *et al* as described above, disclose detection of *Listeria* cells by directly detecting an endogenous enzyme produced by the cells using a substrate for the enzyme (column 1, lines 10-16) wherein the endogenous enzyme is beta-glucosidase and corresponding substrates comprises chemiluminescent 1,2 dioxetane.

Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1), however, differ from the instant application in failing to disclose that the substrate for beta glucosidase comprises a compound selected form the group consisting of {(4-(2-phenoxyethoxy)-4-(3-phosphoryloxy-4-chlorophenyl)}spiro{1,2-dioxetane-3, 13'-tricyclo{7.3.1.0 ^{2,7}}tridec-2,7-ene} and salts thereof.

Giri discloses a highly sensitive chemiluminescent 1,2-dioxetane system which can achieve a detection level as low as attogram of enzyme. (column 1, lines 22-25). Giri discloses that the invention enables the detection of galactosidase, alkaline phosphatase and other enzymes at attogram level and comprises a stable 1,2 dioxetane derived from a spiro-fused ketone with carbon-carbon double bond and a polymeric enhancer (see the reaction scheme in column 9 and column 12, lines 26-29). Giri discloses several 1,2-dioxetane compounds (column 14, lines 29-52) and a particular compound disclosed as useful for the practice of his invention is {(4-(2-phenoxyethoxy)-4-(3-phosphoryloxy-4-chlorophenyl)}spiro{1,2-dioxetane-3,13'-tricyclo{7.3.1.0 ^{2,7}}tridec-2,7-ene} (see claims 2 and 5), which is the same as the compounds of claims 9 and 26 of instant application.

Therefore, given the above fact that the chemiluminescent system of Giri is highly sensitive, which can detect enzymes at an attogram level, it would have been obvious to one of ordinary skill in the art at the time the invention was made to try the highly sensitive chemiluminescent system of Giri for the detection of immobilized *Listerial* cells of Basbøll *et al*, with the expectation of improving the detection sensitivity, with a reasonable expectation of success because Giri discloses that the system can be used for detection of other enzymes besides beta-galactosidase and alkaline phosphatase (column 12, lines 26-29).

As for kit claim 26, Bronstein et al disclose components in a kit (column 5, lines 10-15). However, the packaging of components in kit form is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

11. Claims 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) as described above and further in view of each of Batt *et al* US 5,294,537), Gangne *et al* (Journal of Clinical Microbiology 1998), Gilpatrick *et al* (J. Virology 2000) and Bao *et al* (Biol. Proced. Online 2002).

See above teaching of Basbøll *et al* (US 5,648,227) in view of Bronstein *et al* (US 6,586,196 B1) and Chen *et al* (US 6,355,449 B1) for chemiluminescent detection of

microorganisim (e.g. *listeria spp*) using antibody bound to a solid phase (Basbøll *et al;* column 2, line 65 and claim 14).

Basbøll *et al* (US 5,648,227) disclose blocking of antibody bound solid phase (i.e. aging) with BSA (i.e. a protein) for 30 minutes (column 11, lines 46-51 and column 12, lines 48-51) to inhibit non-specific binding but, however, differ from the instant application in failing to disclose that the solid phase is blocked with a protein (or with a denatured protein) for 12-48 hours.

Batt *et al,* in a detection assay for Listeria monocytogenes, disclose blocking of antibody bound solid phase (i.e. an ELISA plate bound to an antibody) with 0.1% BSA 30 minutes and storing (aging) the ELISA plate at 4°C in the presence of 0.1% BSA to inhibit non-specific binding (column 4, lines 55-60).

Gagne *et al* disclose selective isolation and detection of a microorganism by capture of the microorganism using immunomagnetic beads (see abstract). Gagne *et al* disclose aging of the imunomagnetic beads with 0.1% BSA at room temperature for 30 minutes and then at 4°C until use to inhibit non-specific binding (page 251, second paragraph of right column).

Gilpatric *et al* disclose that magnetic bead surface after immobilizaiton of antibody and washing, the antibody coated beads are aged (i.e. incubated/stored) in the presence of BSA at 4°C until use (page 71, paragraph 2.4.).

Bao *et al* disclose antibody coated solid phase blocked with heat-denatured BSA to inhibit non-specific binding in subsequent steps.

Therefore, give the fact that BSA and heat-denatured BSA are very common and known in the art to block antibody coated solid substrate for inhibition/reduction of non-specific binding and antibody coated surface are aged (incubated/stored) in BSA for a period of time until use, to reduce non-specific binding, it would be obvious to one of ordinary skill in the art at the time the invention was made to block/age antibody coated surface with BSA or denatured BSA for a period of time sufficient to block/inhibit non-specific binding, with a reasonable expectation of success. Moreover, as evidence from the wide range of aging period (12-48 hours and more; see claims 13-15), the aging period of antibody coated inert surface with a protein is not critical to the practice of this invention and the optimum aging period for avoiding non-specific binding can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 223, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable is a known process is ordinary within the skill of the art." Application of Boesch, 617 F.2d 272,276,205 USPQ 215, 218-219 (C.C.P.A. 1980).

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Examiner, Art Unit 1641